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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,338	11/14/2000	Yoshiyuki Ueno	1110-0279P	3959

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EXAMINER
WINKLER, ULRIKE

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 07/15/2003

9

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/700,338	Applicant(s) UENO, YOSHIYUKI	
	Examiner Ulrike Winkler	Art Unit 1648	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *8 and 10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *8 and 10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Response filed May 9, 2003 (Paper No. 8) in response to the Office Action of October 2, 2003 is acknowledged and has been entered. Claims 8 and 10-16 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Claim Rejections - 35 USC § 103

The rejection of claims 8, 10-16 under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Nature of Medicine, 1997) in view of Harada et al. (Hepatology 1997, see IDS) and further in view of Shirakawa et al. (U.S. Pat. No. 6,114,507) **is maintained** for reasons of record.

Applicant's arguments have been fully considered but fail to persuade. Applicants have focused their response using a reference that indicates there is no change in the CD95/Fas in primary biliary cirrhosis vs. normal liver. Applicants specifically cite Graham et al. (page 556, 2nd column lines 5-8) to indicate that the Fas-mediated apoptosis mechanism is unlikely in view of the low levels of Fas expressed on biliary epithelial cells. Applicant's bases their argument that low level of expression would prevent apoptosis from being mediated through the CD95/Fas pathway. Applicants are arguing that the Fas pathway is not powerful, however, the applied art establish the contrary, where Fas is tied to disorders mediated by the Fas apoptosis pathway. The statement that something is unlikely to occur is opinion by the author and is based soley on the low level of expression of CD95/Fas on these cells. It must be emphasized that arguments of

counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964).

The same paragraph cited by Applicant's (page 556, 2nd column lines 8-12) continues to state that this mechanism (Fas apoptosis) has been invoked for a number of inflammatory disease of the liver, especially viral hepatitis and ligation of constitutive expressed Fas/CD95 on hepatocytes by antibodies results in rapid apoptosis. The reference indicates there is no change in the expression Fas/CD95 in primary biliary cirrhotic livers (note a change in the level of CD95/Fas is not claimed). However, the reference goes on to say that they have shown the presence of proteins involved in executing apoptosis in primary biliary epithelial cells which is consistent with previous reports of apoptosis of these cells (see page 556, 2nd column lines last paragraph). The reference has not provided any teaching that would suggest that CD95/Fas are not present on the primary biliary epithelial cells. The rejection by the Office is based on establishing that CD95/Fas is present on the primary biliary epithelial cells. Based on what was known in the art at the time of the invention was filed the Fas molecule is a known powerful molecule involved in the induction the apoptosis death pathway. One of ordinary skill would have been motivated to prevent the crosslinking of CD95/Fas in order to prevent induction of the death pathway.

The instant invention is drawn to a method of preventing and treating **hepatic cirrhosis** (biliary cirrhosis, primary biliary cirrhosis) **or bile duct disappearance syndrome** (caused by an

immunological mechanism) (claims 8, 14-16). Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22).

Kondo et al. teaches that administration of the soluble form Fas into HbsAg transgenic mice prevented CTL-induced liver disease. The reference indicates that the administration of anti-Fas antibodies to mice causes acute liver failure by inducing apoptosis in hepatocytes (see page 409, column 1 1st paragraph) The studies showed that blocking the Fas-induced cytotoxicity prevents the development of hepatitis (page 411, column 1, last paragraph). The results show that apoptosis of hepatocytes in the initial stages of hepatitis is mainly mediated by Fas-L. The involvement of the Fas system in human fulminate hepatitis is is proven. The reference clearly suggest using soluble form of Fas, anti-FasL antibody or inhibitors of Fas mediated apoptosis (see page 412 columns 2,last paragraph).

Harada et al. teach that Fas is expressed on a broad range of human tissue, including biliary epithelial cells. The reference teaches that interlobular bile ducts of primary biliary cirrhosis frequently expressed CD95 (Fas) antigen in a cytoplasmic and membranous pattern, in addition a high intensity of CD95 ligand (Fas-ligand) positive mononuclear cells was found in the same pathology samples (see page 1404, column 1, paragraph 2). The findings demonstrate that biliary epithelial cells in primary biliary cirrhosis undergo apoptosis in response to the Fas/Fas ligand mediated cross linking, suggesting that apoptosis is involved in the progression of bile duct injury and loss. The reference does teach using a Fas antagonist to treat the primary biliary cirrhosis.

Shirakawa et al. teach an antibody directed to Fas ligand (see claim 1) and a method of treating systemic or topical pathological conditions caused by the interaction of Fas ligand with

Fas. The method comprises administering to a patient a therapeutically effective dose of an anti-Fas ligand antibody, which suppresses Fas ligand induced apoptosis (see claim 22). The reference does not expressly teach treating primary biliary cirrhosis.

The combination of references teaches utilizing a Fas antagonist for the prevention of Fas/Fas ligand interaction *in vivo* in an animal/patient. The references teach that Fas is present in the cells involved in primary biliary cirrhosis. Bile duct disappearance syndrome is caused by primary biliary cirrhosis (see specification page 13, lines 18-22) therefore the same mechanism that are involved in primary biliary cirrhosis would be involved in bile duct disappearance syndrome. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to treat primary biliary cirrhosis by disrupting the Fas/Fas ligand interaction that leads to apoptosis of the cells involved in primary biliary cirrhosis as taught by Harada et al. One having ordinary skill in the art would have a high expectation of success in utilizing Fas antagonists for the purpose of treating bile duct disappearance syndrome and primary biliary cirrhosis in a patient using the antagonist and treatment methods taught by either Kondo et al. and Shirakawa et al.

Therefore the instant invention is obvious Kondo et al. in view of Harada et al. and further in view of Shirakawa et al.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 703-308-8294. The examiner can normally be reached M-F, 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 703-308-4027.

The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for informal communications use 703-308-4426.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ulrike Winkler, Ph.D.

JAMES HOUSEL 7/14/03
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600